



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

**MEMORANDUM**

April 26, 2012  
TXR # 0056209

**SUBJECT:** **Bifenthrin:** Summary of Hazard and Science Policy Council (HASPOC)  
Meetings of January 4, 2012, March 8, 2012, and April 26, 2012:  
Recommendations on the need for sub-chronic inhalation and 90-day dermal  
toxicity studies.

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**Petition No.:** N/A  
**Risk Assessment Type:** N/A  
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**FROM:** Deborah Smegal, MPH and Kristin Rury, MPH  
Executive Secretaries, HASPOC  
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**THROUGH:** Jess Rowland, Co-Chair  
Anna Lowit, Ph.D, Co-Chair  
HASPOC  
Health Effects Division (7509P)

**TO:** William Irwin, Ph.D., Toxicologist  
Michael Metzger, Branch Chief  
Registration Action Branch 5  
Health Effects Division (7509P)

**MEETING ATTENDEES:**

**January 4, 2012 Meeting**

**HASPOC Members:** Jonathan Chen, Jeff Evans, Ray Kent, John Kough, Anna Lowit, Mike Metzger, Elissa Reaves, Jess Rowland, Jessica Ryman, PV Shah, Debbie Smegal, Vicki Dellarco, and Karen Whitby

Other Attendees: Lisa Austin, Joel Wolf, and Wade Britton

Presenter: William Irwin

### **March 8, 2012 Meeting**

HASPOC Members: Jonathan Chen, Jeff Evans (phone), Ray Kent, Anna Lowit, Mike Metzger, Elissa Reaves, Jess Rowland, Jessica Ryman, Debbie Smegal, Vicki Dellarco, John Kough, Julie Van Alstine, and Kristin Rury.

Other Attendees: Ed Scollon, Zaida Figueroa, and Margarita Collantes,

Presenter: William Irwin

### **April 26, 2012 Meeting**

HASPOC Members: Jonathan Chen, Ray Kent, Anna Lowit, Mike Metzger, Elissa Reaves, Jess Rowland, Jessica Ryman, Julie Van Alstine, and Kristin Rury.

Other Attendees: Debbie Smegal, Ed Scollon, Zaida Figueroa, and Margarita Collantes,

Presenter: William Irwin

## **I. PURPOSE OF MEETINGS:**

The HED Hazard and Science Policy Council (HASPOC) met on January 4, 2012, March 8, 2012, and April 26, 2012 to discuss whether a sub-chronic inhalation toxicity study and a 90-day dermal toxicity study are required to address the concern for repeated dermal and inhalation exposures resulting from the proposed and registered uses of bifenthrin.

## **II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:**

Bifenthrin is a pyrethroid insecticide/miticide used to control termites and insects in both agricultural and residential settings. Bifenthrin is currently registered as emulsifiable concentrate (EC), wettable-powder (WP), granular (G), and flowable-concentrate (FIC) formulations. Bifenthrin is registered for use by occupational handlers on a variety of agricultural commodities, and by occupational and residential handlers on turf and indoor environments (crack and crevice). Exposure to bifenthrin is expected to be short- and intermediate-term durations for occupational handlers and short-term for residential handlers and following use in residential settings. Bifenthrin may be applied with handheld, ground, and aerial equipment.

In previous risk assessments for bifenthrin, inhalation risk estimates were based on points of departure (PODs) established from oral toxicity studies. Based on the 2008 risk assessment, the Margins of Exposure (MOE) for inhalation exposure from occupational and residential uses exceeded HED's Level of Concern (LOC) ( $\geq 100$  for adults and  $\geq 300$  for children) and ranged

from 830 to 210,000 for currently registered uses (W. Wassell, D352419, 05/14/2008). Mixing/loading liquids for aerial application on proposed uses on grass grown for seed (forage/hay) resulted in the highest dermal exposure to bifenthrin. The MOE was 290 for dermal exposure and 9,800 for inhalation exposure with an Aggregate Risk Index (ARI) of 2.2 for the combined dermal and inhalation exposures. Dermal MOEs > 100 are achieved on Day 0 for all potential post-application activities and, therefore, are not of concern.

Neurotoxicity is the most consistently observed finding throughout the bifenthrin toxicity database, and neurotoxic effects provide the most sensitive endpoints for deriving PODs for risk assessment. Bifenthrin toxicology database provides no evidence of enhanced toxicity with increase in exposure (treatment) time since comparable No Observed Effect Levels (NOAELs) were obtained following acute, subchronic and chronic exposures. Comparable PODs were established in the acute (BMDL=3.1 mg/kg), subchronic (NOAEL=2.9 mg/kg/day) and the carcinogenicity (NOAEL = 3.0 mg/kg/day) studies.

Based on the new endpoints (US EPA. Bifenthrin - ToxSAC Meeting Report, October 6, 2011), for acute dietary and short-term inhalation exposure risk assessment, the POD is a BMDL<sub>1SD</sub> of 3.1 mg/kg based on reductions in motor activity seen at a BMD<sub>1SD</sub> of 4.1 mg/kg (Wolansky *et al* 2006). The POD for short-term dermal exposure risk assessment is a BMDL<sub>10</sub> of 96.3 mg/kg/days based on observations of clinical signs (staggered gait and exaggerated hindlimb reflex) at a BMD<sub>10</sub> of 187.0 mg/kg/day in a 21-day rat dermal toxicity study.

Metabolism is the major route of detoxification for bifenthrin. Hydrolysis of the ester linkage and oxidative metabolism by the liver are the primary routes of metabolism. Exposure via the inhalation route bypasses the liver and therefore has the potential for increased toxicity.

### III. INHALATION STUDY WAIVER REQUEST

#### ***A. Requirement for the inhalation study***

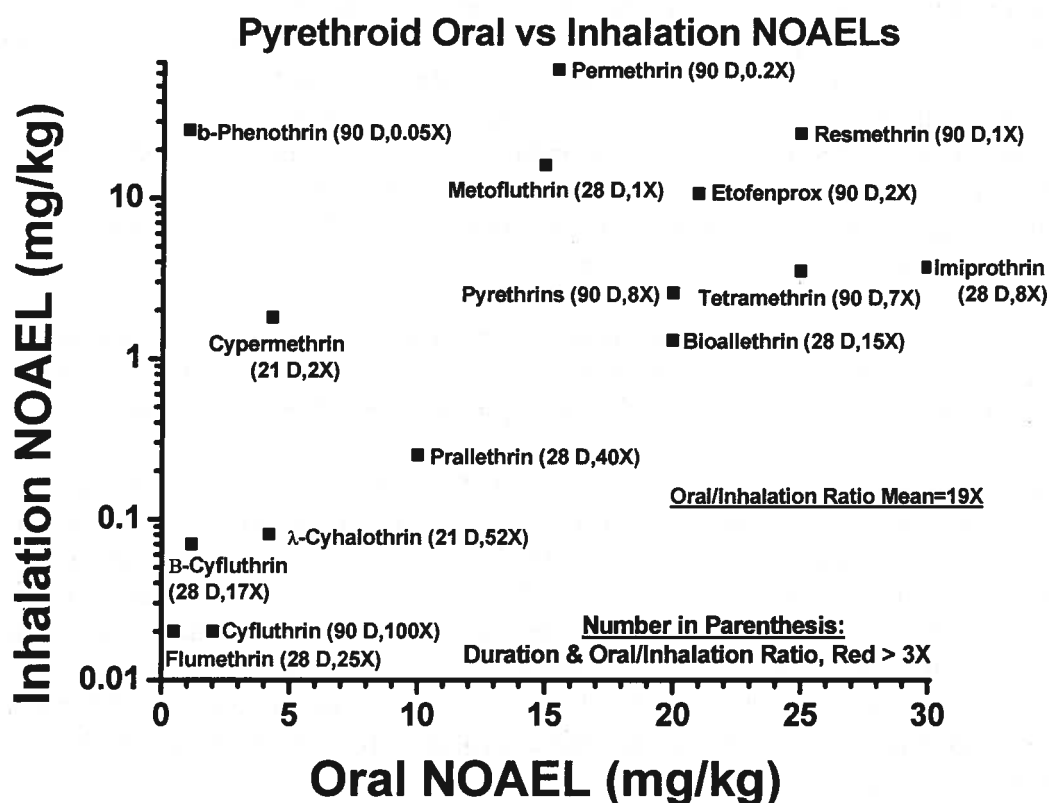
Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical-chemical properties:** Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. Bifenthrin has a low vapor pressure ( $2.41 \times 10^{-5}$  Pa at 25 °C). However, low vapor pressure and/or Henry's law constant ( $7.2 \times 10^{-3}$  atm·m<sup>3</sup>/mol) does not preclude exposure to aerosolized droplets or particles/dusts.
2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. It is, however, acknowledged that airblast and aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may contribute to spray drift. Mixing and loading of granules for aerial applications led to the highest inhalation exposure to bifenthrin, with an inhalation MOE of 830. For residential handlers, treating structural wood with bifenthrin using a paintbrush resulted in the highest inhalation exposure (MOE = 23,000).
3. **Margins of Exposure (MOEs):** The MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides, but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the level of concern will be considered in combination with other factors discussed here. For short-term inhalation exposure risk assessment, an oral POD of 3.1 mg/kg is used for calculating the MOEs. Mixing and loading of granules for aerial applications led to the highest inhalation exposure to bifenthrin, with an inhalation MOE of 830.
4. **Toxicity:** Bifenthrin is a neurotoxic insecticide that belongs to the pyrethroid class of chemicals. Pyrethroids induce neurotoxicity by interacting with sodium channels located in nerve cells, causing hyperpolarization and eventually blocking nerve conductance. Tremors are the most consistent effect across all toxicity studies. The most robust study (Wolansky et al 2006) monitored decreased locomotor activity, and is the basis of the PODs used for risk assessment. Based on bifenthrin's toxicity profile, the severity of effects from oral exposure do not appear to increase substantially over longer durations. Bifenthrin has a moderate order of acute toxicity via the oral route (Category II) and a low order of acute toxicity via the dermal route (Category III) of exposure. The acute lethal inhalation study classifies bifenthrin as Category III, with a combined LC<sub>50</sub> value of 1.01 mg/L (male result is 1.1 mg/L and female result is 0.8 mg/L). Acceptable studies on the end-use products are also available. Formulated bifenthrin is neither an eye nor skin irritant, nor is it a dermal sensitizer.

For considering a waiver request for inhalation toxicity study, the Agency will evaluate other pesticides which share the same mode of action (MOA) and/or are in the same class. These pesticides can provide important information with respect to potential inhalation toxicity. Specifically, if other similar pesticides show inhalation toxicity

studies to be more sensitive, an inhalation toxicity study may be required regardless of MOE, depending on the exposure profile. EPA conducted a comparative analysis of repeat-dosing inhalation and oral studies for 15 pyrethroids to determine the relative route-specific toxicity. The inhalation NOAELs were on average 19X lower than the oral NOAELs, indicating that the pyrethroids are more potent following inhalation exposure. Similar results were obtained when comparing the LOAELs. Below is a graphic depiction of this analysis. The inhalation studies for resmethrin and the pyrethrins do not have NOAELs, so the study LOAELs were reported instead.



Based on a WOE approach considering of all the available hazard and exposure information for bifenthrin, the HASPOC concluded that an inhalation study is required. This decision was based on the following factors: (1) concern for the MOE (> 830) for inhalation exposure in occupational and residential settings; (2) the physical chemical properties and the volatility of the compound; 3) the neurotoxic potential and the mode of action for the pyrethroid-induced toxicity; and (4) data for other pyrethroids that show that this pesticide class in general is approximately 19 fold more potent following inhalation exposure than oral exposure.

#### B. *Duration of the Inhalation Study*

The neurotoxic MOA for pyrethroids has a rapid temporal pattern with peak time of effect for bifenthrin of 4 to 8 hours, depending on the vehicle, vehicle volume, and route of administration. Recovery occurs within 24 hours of exposure. When considering the appropriate duration of the required inhalation study for bifenthrin, the team evaluated the sensitivity of respiratory effects in the existing inhalation studies for pyrethroids.

Of the available pyrethroid inhalation toxicity studies (approximately 15), signs of respiratory toxicity were seen for several chemicals. These signs included: irregular respiration, histopathology in nasal turbinates, decreased lung function, and larynx hyperplasia. In general, respiratory toxicity for the pyrethroids occurred at the same doses as other systemic signs, indicating that the respiratory endpoints were often not more sensitive indicators of toxicity. Inhalation toxicity studies with pyrethrin formulation (57% active ingredient; a.i.), showed hyperplasia in the larynx at 2.56 mg/kg/day while systemic effects of tremors occurred at 26.9 mg/kg/day, although, the formulation's 43% impurity content may be responsible for the respiratory effects. The two available bifenthrin formulation LD<sub>50</sub> studies did show signs of respiratory toxicity, including difficulty breathing, at a high dose of 324 mg/kg/day. However, the other components in the bifenthrin formulations (i.e. surfactants, mineral oil, etc.) may enhance or suppress the toxicity of bifenthrin.

Although some exceptions are noted, neurotoxicity was the most prominent finding across the bifenthrin and pyrethroid toxicity databases. Respiratory effects are not expected to be seen at lower doses than neurotoxicity; tremors are common in the bifenthrin database.

**Based on the factors discussed above, the HASPOC concluded that a subchronic inhalation toxicity study is not required at this time based on the current/proposed use patterns. *The HASPOC is confident that neurotoxicity is the primary MOA, and thus a single-day study is appropriate to assess inhalation toxicity of bifenthrin; a sub-chronic inhalation toxicity study is not needed at this time.*** The acute inhalation toxicity study should evaluate all parameters as stipulated in the Guideline 870.6200a (acute neurotoxicity study). It is recommended that the registrant submit the study protocol for Agency review. **However, changes in the use pattern or in the knowledge about the toxicological profile will result in the re-evaluation of this decision by the Agency.**

#### IV. 90-DAY DERMAL STUDY WAIVER REQUEST

With respect to considering whether a 90-day dermal study is required, the HASPOC used a weight of the evidence approach. This WOE approach considers:

- 1. Use pattern & exposure scenarios:** Two 21-day dermal toxicity studies are available for bifenthrin, in the rat and rabbit. However, because there is a potential for repeated exposure to bifenthrin longer than 90 days from use in occupational and residential settings, the HASPOC discussed whether a 90-day dermal toxicity study is best suited to assess the longer exposure concerns. There is also a potential for post-application short-term dermal exposures from entering fields, turf, and indoor areas treated with bifenthrin. Bifenthrin is formulated as an EC, FLC, WP, and G products.

2. **Margins of Exposure (MOEs):** The MOE estimates for dermal scenarios were calculated using an oral POD of 96.3 mg/kg/day. Mixing and loading liquids for aerial application on proposed uses on grass grown for seed (forage/hay) resulted in the highest dermal exposure estimates to bifenthrin (dermal MOE of 290). All occupational and residential handler MOEs exceeded the Agency's LOC (LOC = 100). Dermal MOEs > 100 are achieved on Day 0 for all potential post-application activities and, therefore, are not of concern.
3. **Toxicity:** There are two 21-day dermal studies for bifenthrin; one in the rat - the most sensitive species, and one in the rabbit. The rat dermal toxicity study had a LOAEL of 93 mg/kg/day based on staggered gait in males, and exaggerated hind limb flexion in females. The NOAEL was 47 mg/kg/day. The rabbit dermal toxicity study had a LOAEL of 442 mg/kg/day based on a loss of muscle coordination and increased tremors. The NOAEL was 88 mg/kg/day. The rat dermal toxicity study BMDL<sub>10</sub> was 96.3 mg/kg/day, similar to the NOAEL seen in the rabbit dermal toxicity study. The rat dermal toxicity study BMD<sub>10</sub> was 187 mg/kg/day based on exaggerated hind limb flexion.

As discussed earlier, there was no evidence of enhanced toxicity with increase in exposure (treatment) time since comparable NOAELs were obtained following acute, subchronic and chronic exposures via the oral route. .

**The HASPOC concluded, based on a WOE approach, that a 90-day dermal toxicity study for bifenthrin is not required at this time.** This approach considered the following factors: 1) there are two 21-day day dermal toxicity studies available for bifenthrin; and 2) the toxicity database for bifenthrin shows that following oral exposures toxicity does not increase over time and therefore, a 90-day study may not provide a POD lower than the POD from the 21-day study that is used in the current risk assessment. When taken together, these lines of evidence support the conclusion that a 90-day dermal toxicity study is not needed at this time. If the use pattern changes, the Agency may re-evaluate the need for a 90-day dermal toxicity study.

#### V. SUMMARY OF HASPOC RECOMMENDATIONS:

HASPOC concluded that a special acute inhalation study is required. Therefore, in the absence of a route-specific inhalation study, a 10X database uncertainty factor should be applied to inhalation scenarios only. The HASPOC recommends that the acute inhalation toxicity study protocol include a single exposure via the inhalation route and evaluate parameters specified in both the acute neurotoxicity (870.6200) and the sub-chronic inhalation toxicity (870.3465) studies. This protocol will enable evaluation of toxicity to both the respiratory and nervous system. The protocol must be submitted for Agency review prior to beginning the study.

A 90-day dermal toxicity study is not required for bifenthrin at this time.